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Synthesis of chiral α-hydroxy acids *via* palladium-catalyzed C(sp^3)–H alkylation of lactic acid†

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Herein we report a Pd-catalyzed alkylation of lactic acid with the assistance of 8-aminoquinoline auxiliary. A wide range of alkyl iodides bearing β-hydrogen atoms are compatible with the reaction conditions, providing a practical and straightforward alternative to access chiral α-hydroxy acids (AHAs). The new reactions have been applied for the synthesis of isotope-labeled AHAs and a sugar-containing complex AHA.

Enantiomerically pure α-hydroxy acids (AHAs) are an important class of structural moieties found in natural products and pharmaceuticals.[1] Lactic acid, a naturally occurring AHA, is crucial in various biochemical processes regarding energy storage and conversion.[2] Beyond lactic acid, AHAs containing alkyl groups at the β-position are also prevalent in numerous pharmaceutically important compounds (Fig. 1).[3] AHAs, such as L-leucic acid [(*S*)-2-hydroxy-4-methylpentanoic acid], L-valinic acid [(*S*)-2-hydroxy-3-methylbutanoic acid], and (*S*)-2-hydroxypentanoic acid, are present in a number of biologically important depsipeptides with potent antitumor and antifungal activities.[3a] Some important lipid-type natural products with useful biological activities, including glycolipids, sphingolipids, polyketides, *etc.*, also contain unnatural AHA fragments. For instance, hydrophobic fatty AHAs were found in the natural products cerebroside B_{1a} and cerebroside B_{1b}, which are the active anti-ulcerogenic components in a traditional Chinese herbal medicine.[3b] In addition, chiral AHAs are also versatile building blocks in medicinal and synthetic organic chemistry.[1b]

In recent years, tremendous efforts have been devoted to the use of biomass and its related downstream chemicals as a source of energy and chemical transformations, largely due to their abundance, renewability and low cost.[4] Lactic acid, the simplest chiral AHA, is a platform chemical which can be derived from biomass. Thus, there is a strong impetus to develop chemical transformations that target lactic acid as a valuable chiral synthon.[1] As part of our continuing efforts on Pd-catalyzed functionalization of unactivated C(sp^3)–H bonds of biomass-derived starting materials containing carboxylate functional group (*e.g.*, α-amino acids, fatty acids *etc.*),[5] we envisioned that appropriately protected lactic acid[6] could be used as a feedstock to access chiral AHAs *via* Pd-catalyzed alkylation of β-methyl C(sp^3)–H bonds.

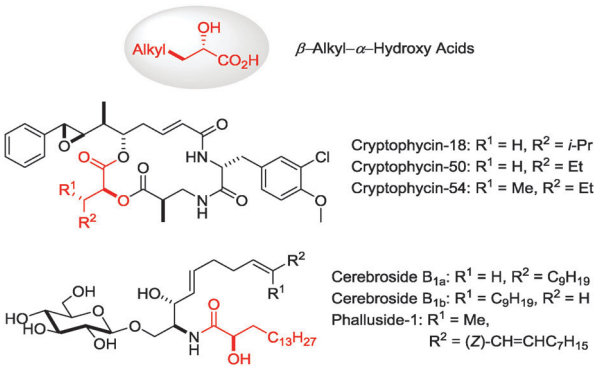

Fig. 1 Natural products containing α-hydroxy acids.

However, despite the significant progress in Pd-catalyzed C–H activation/C–C coupling reactions,[7] the C(sp^3)–C(sp^3) bond formation *via* direct alkylation of C(sp^3)–H bonds with alkyl halides (R_{alkyl}–X), especially those bearing β-hydrogen atoms, remains largely undeveloped.[5b,d,6a,10] Based on the catalytic cycle for C(sp^3)–H alkylation, at least two fundamental challenges for the difficulty are relevant to each coupling partner: (1) aliphatic C(sp^3)–H bonds are chemically more inert, and the selective cleavage of one of the chemically similar C(sp^3)–H bonds is extremely difficult; (2) alkyl halides are reluctant to undergo oxidative addition, and they are prone to participate in many competitive side reactions, such as elimination or hydrodehalogenation.[8] In 2006, Yu reported

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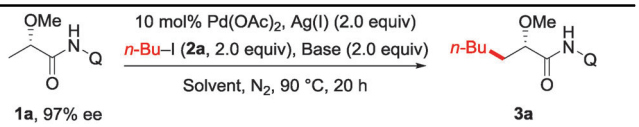
Table 1 Optimization of the reaction conditions[a]



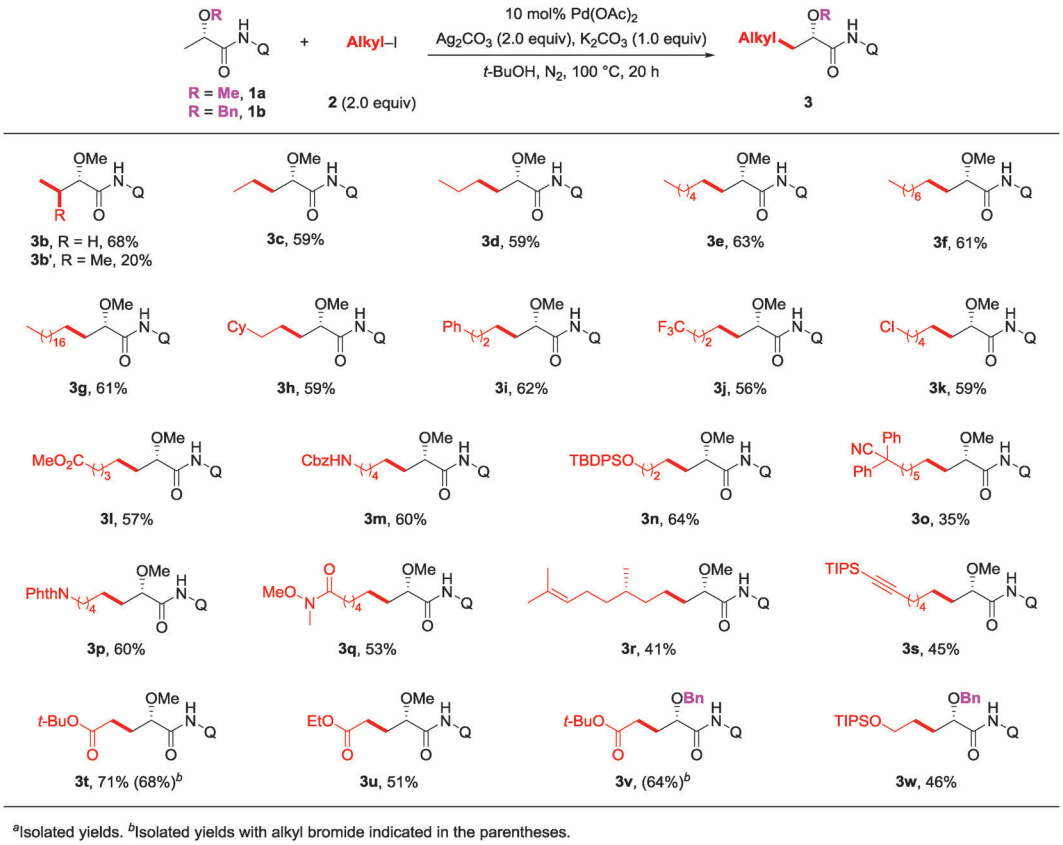
1a, 97% ee — 3a

Entry	Ag(I) salts	Base	Solvent	Yield 3a[a] (%)
1	Ag_2CO_3	—	*t*-AmylOH	<3
2	Ag_2CO_3	KOCN	*t*-AmylOH	34
3	Ag_2O	KOCN	*t*-AmylOH	22
4	AgOAc	KOCN	*t*-AmylOH	Trace
5	Ag_3PO_4	KOCN	*t*-AmylOH	0
6	AgF	KOCN	*t*-AmylOH	0
7	Ag_2CO_3	KOCN	*t*-BuOH	49
8	Ag_2CO_3	KOCN	THF	5
9	Ag_2CO_3	KOCN	AcOET	22
10	Ag_2CO_3	KOCN	PhMe	0
11	Ag_2CO_3	KOCN	DCE	0
12	Ag_2CO_3	Li_2CO_3	*t*-BuOH	<3
13	Ag_2CO_3	Na_2CO_3	*t*-BuOH	33
14	Ag_2CO_3	K_2CO_3	*t*-BuOH	62[c]
15	Ag_2CO_3	Rb_2CO_3	*t*-BuOH	61
16	Ag_2CO_3	Cs_2CO_3	*t*-BuOH	35
17[b]	**Ag_2CO_3**	**K_2CO_3**	***t*-BuOH**	64 (22, 94% **ee**)[c,d,e]
18	—	K_2CO_3	*t*-BuOH	0

[a] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] 100 °C, 1.0 equiv. K_2CO_3. [c] Isolated yield. [d] Recovery yield of the starting material **1a** recovered. [e] Enantiomeric excess (ee values) was determined by HPLC on a chiral stationary phase (see the ESI).

the first Pd-catalyzed alkylation of unactivated C(sp^3)–H bonds using alkylboronic acids or methylboroxines.[9] Compared to tin- or borane-based alkylation reagents, alkyl halides are cheaper, more readily available, and less toxic. In 2010, Daugulis introduced the Pd-catalyzed alkylation of C(sp^3)–H bonds with primary alkyl iodides assisted by the bidentate AQ auxiliary.[6a] In 2013, the Chen group demonstrated a Pd-catalyzed, $(BnO)_2PO_2H$-enabled alkylation of methyl C(sp^3)–H bonds with alkyl iodides with the assistance of the picolinamide auxiliary.[10a] Shortly after, Chen and our laboratory achieved the Pd-catalyzed alkylation of α-amino acid derivatives with alkyl halides by employing the AQ auxiliary to access various unnatural β-alkylated α-amino acids.[5b,d,10b] With these precedents, we were encouraged to investigate whether this efficient protocol could be applied to the alkylation of more challenging, yet synthetically important lactic acid derivatives. Herein, we report the Pd-catalyzed alkylation of appropriately protected lactic acids for the synthesis of unnatural AHAs by using the 8-aminoquinoline (AQ) directing group.[11,12] A broad range of alkyl iodides bearing β-hydrogen atoms are compatible with the protocol. Moreover, the reaction also allows facile access to more complex molecules with sugar groups.

Our studies commenced with the application of reaction conditions previously reported by our group for the alkylation of α-amino acid derivatives.[5b] Unfortunately, these protocols were found to be completely incompatible with the butylation



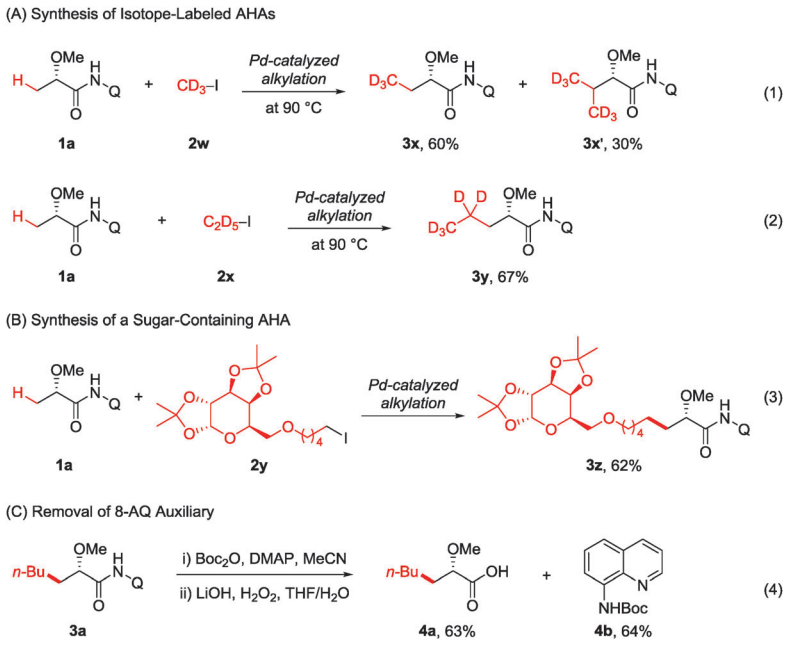
[a]Isolated yields. [b]Isolated yields with alkyl bromide indicated in the parentheses.

Fig. 2 Substrate scope of alkylation of lactic acid.

of the lactic acid-derived substrate **1a**. Only trace amount of desired product **3a** was observed when Ag_2CO_3 was used as the sole iodide scavenger (Table 1, entry 1). Previously, we have found that the combination of silver salts with inorganic bases could also improve the yield, and the cyanate anion has a unique effect on the alkylation reaction.[5b] The combination of Ag_2CO_3 and KOCN[5d] gave the butylated product **3a** in 34% yield (entry 2). Further screening of the silver salts indicated that Ag_2CO_3 was optimal (entries 2–6). *t*-BuOH was found to give the highest yield (entries 7–11). We envisioned that the choice of a suitable base should be crucial for the success of this transformation. To this end, we screened a series of alkali metal carbonates (entries 12–16) and acetates (see the ESI,† for details) and found that different cations exhibit a significant effect on the reaction, where potassium and rubidium were the most effective (entries 14 and 15), while different counterions showed no obvious influence on the reaction (see the ESI,† for details). With the observation that a catalytic amount of K_2CO_3 still led to an acceptable 53% yield of **3a** (see the ESI,† for details), an alternative explanation is that the potassium cation additive not only plays the role as a simple base for C–H activation, but also possibly inhibits the potential coordination of α-methoxyl with palladium catalysis. When the reaction was conducted at 100 °C, the desired product **3a** was obtained in 64% yield (entry 17, with 22% **1a** recovered). Finally, no desired product was observed in the absence of Ag_2CO_3, indicating that the halide scavenger was indispensable to the reaction (entry 18). It was worth noting that the alkylation product was obtained with only a slight racemization (**1a**, 97% ee; **3a**, 94% ee).

under the optimized reaction conditions. Generally, linear and branched primary alkyl iodides reacted efficiently with **1a**, affording the corresponding alkylated products in good yields (**3b–3i**). Consistent with previous results, MeI was identified to be a superior coupling partner, giving the mono- and di-methylated products in 68% (**3b**) and 20% (**3b′**) yield, respectively.[5b] Moreover, a broad range of functional groups, including trifluoromethyl (**3j**), chloro (**3k**), methoxycarbonyl (**3l**), Cbz-protected amino (**3m**), silyl (**3n**), cyano (**3o**), Phth-protected amino (**3p**), Weinreb amide (**3q**), alkenyl (**3r**) and TIPS-protected terminal alkynyl (**3s**), were well tolerated under the reaction conditions. However, the alkylated products **3o**, **3r** and **3s** were obtained in reduced yields, largely due to the competing coordination with the palladium catalyst. α-Haloacetate esters bearing no β-hydrogen atoms have been reported to exhibit relatively higher reactivity by avoiding palladium-involved β-hydrogen elimination or base-promoted eliminations of alkyl halides.[5b] Indeed, we were pleased to find that both *tert*-butyl bromoacetate and iodoacetate showed high efficiency and gave the desired product **3t** in high yield.

In addition, different protecting groups of hydroxyl were also examined to showcase the practicality of the alkylation protocol. Notably, the easily removable benzyl ether substrate **1b** was also compatible with the reaction. For example, the corresponding alkylated products **3v** and **3w** were obtained in moderate to good yields when hydroxyl was protected with benzyl. The alkylated product **3w** could be readily converted into (*S*)-α-benzyloxy-δ-valerolacton, which is a useful intermediate in the chemical synthesis of polyether toxins.[13] Notably, most of the starting lactic acid derivatives were recovered when the products were isolated in low yields.



With the optimal conditions for the alkylation of lactic acid-derived amide **1a** in hand, we next investigated the scope of alkyl iodides (Fig. 2). A variety of alkyl iodides proceeded smoothly

Isotope-labeled compounds are of great value in the study of biochemical processes. We were pleased to find that the alkylation protocol could also be used for the synthesis of

deuterated AHAs. The methylation of the lactic acid-derived amide **1a** with d_3-MeI gave a mixture of monomethylation product **3x** (60%) and dimethylation product **3x′** (30%), which could be easily separated by chromatography (entry 1). In addition, ethylation of **1a** with d_5-EtI gave the corresponding isotope-labeled product **3y** in 67% yield (entry 2). Therefore, this protocol provided an efficient access to isotope-labeled α-hydroxyl acids. Moreover, the alkylation protocol was also compatible with more complicated coupling partners. The coupling of **1a** with galactose-derived alkyl iodide (**2y**) under the standard conditions of alkylation afforded the corresponding product **3z** in 62% yield (entry 3). These examples demonstrated the further synthetic potentials in the late-stage modification of complex molecules. At last, the AQ auxiliary could be easily removed in good yield under mild conditions.[14] As shown in entry 4, the protection of the secondary amide of **3a** with Boc_2O, followed by the treatment of the resulting tertiary amide with $LiOH/H_2O_2$, gave the corresponding α-methoxy carboxylic acid **4a** in 63% yield with BocNHQ recovered in 64% yield.

In conclusion, we have developed the palladium-catalyzed AQ-directed alkylation of lactic acid derivatives for the synthesis of chiral α-hydroxy acids (AHAs). Although the direct C(sp^3)–H alkylation of α-amino acids has been well investigated and found tremendous applications in organic synthesis, the reaction here represents the first systematic investigation of the direct C–H alkylation of lactic acid, providing a practical alternative to chiral AHAs. A wide range of alkyl iodides bearing synthetically useful functional groups are well tolerated. The synthetic importance of these novel protocols was further demonstrated by the synthesis of isotope-labeled AHAs and a sugar-containing complex AHA.

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